## REMARKS/ARGUMENTS

### Status of the Application

Claims 49-119 are pending with the entry of this amendment. No new matter was added. Applicants respectfully request entry of the amendments which are presented herein.

- Claims 49-63, 86-115, 118-120 and 123-124 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-20 of U.S. Patent No. 5,719,060.

- Claims 49-124 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-46 of U.S. Patent No. 5,894,063.

- Claims 49-55, 57, 59, 62-71, 73-74, 76, 78, 81, 84, 86-93, 95, 97, 100, 101 and 105-113 were rejected under 35 U.S.C. § 102(b) over Applicants' allegedly admitted prior art, Van Breemen et al.

- Claims 49-124 were rejected under 35 U.S.C. § 102(b) over Applicants' allegedly admitted prior art, Benninghoven et al.

- Claims 56, 58, 60-61, 72, 75, 77, 79-80, 82-83, 85, 94, 96, 98-99, 102-104 and 114-124 were rejected under 35 U.S.C. § 103(a) over Van Breemen et al.

### Support for Amendments

Support for the amendments can be found throughout the specification and the claims, as originally filed. Support for the non-metallic surfaces can be found throughout the specification, specific examples can be found on page 10, lines 12-18, page 12, lines 19-21, and page 13, lines 6-9. Support for the term "matrix material" can be found throughout the specification, specific examples can be found on page 6, line 12, page 9, lines 15-19, and page 26, lines 16-18. The amendments do not introduce new matter. As a convenience to the Examiner, a marked-up version of the changes made to claims by the current amendment is attached hereto as an appendix A. For the convenience of the Examiner, Applicants have included as appendix B a copy of the claims pending after entry of this amendment.

**Obviousness-type Double Patenting Rejections**

Claims 49-63, 86-115, 118-120 and 123-124 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-20 of U.S. Patent No. 5,719,060. Claims 49-124 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-46 of U.S. Patent No. 5,894,063.

These rejections are traversed. Applicants note that the '060 patent has an apparent patent term through February 17, 2015 and the '063 patent has an apparent patent term through April 13, 2016. A patent issuing from the present application would normally expire on May 28, 2013. Therefore, applicants expect no loss in patent term as a result of filing a terminal disclaimer in the present application. Without agreeing to the substance of the Examiner's rejection and in the interest of expediting the prosecution, Applicants submit herewith a terminal disclaimer over the '060 and '063 patents.

**Rejections Under 35 U.S.C. § 102**

**A. Van Breemen et al.**

Claims 49-55, 57, 59, 62-71, 73-74, 76, 78, 81, 84, 86-93, 95, 97, 100, 101, and 105-113 were rejected under 35 U.S.C. § 102(b) as being anticipated by Van Breemen et al. Examiner states that Van Breemen et al. teaches a method which "involves the vaporization and ionization of a small sample of matter" using a probe with a Vespel (polyimide) tip to present the analyte sample to the energy source for ionization. Applicants respectfully traverse this rejection. Anticipation of a claim is only established where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The teachings employed by Van Breemen do not anticipate the claims found in the present application. The claims in the present application are directed to methods and systems involving probes comprising non-metallic surfaces for desorbing and ionizing macromolecular analytes. First, the method of Van Breemen does not involve analysis of macromolecular analytes. Second, the probe taught by Van Breemen is a metallic (stainless

steel) probe containing a Vespel rod.

In order to further the prosecution of the present application, Applicants have amended claims 49, 64 and 86 without acquiescence and prejudice to indicate the non-metallic surfaces of the present invention are selected from the group consisting of glass, ceramic, polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran. Vespel is not among this group. Therefore, the rejection of the claims is improper, and withdrawal of the rejection is respectfully requested.

**B. Benninghoven et al. (U.S. Patent 4,468,468)**

Claims 49-124 were rejected under 35 U.S.C. § 102(b) as being anticipated by Benninghoven et al. According to the Examiner, Benninghoven teaches a method "using time of flight mass spectrometry where the sample is bound to the probe by physical adsorption (van der Waals forces), chemisorptions, enzyme binding or antibody/antigen binding."

Applicants respectfully traverse this rejection because this prior art fails to anticipate the claims in the present application as it does not articulate every element of these claims. The Benninghoven patent uses a metallic (stainless steel) sample holder or probe that is covered with nitrocellulose lacquer, celluloid lacquer or Formvar and thus does not anticipate the use of non-metallic probes in the present application.

In order to further the prosecution of the present application, Applicants have amended claims 49, 64 and 86 without acquiescence and prejudice to indicate the non-metallic surfaces of the present invention. Therefore, since these express limitations are absent in the Benninghoven patent, the Benninghoven patent is precluded from anticipating the present claims. Thus, the rejection of claims 49-124 is improper, and withdrawal of the rejection is respectfully requested.

**Rejections Under 35 U.S.C. § 103**

Claims 56, 58, 60-61, 72, 75, 77, 79-80, 82-83, 85, 94, 96, 98-99, 102-104 and 114-124 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Van Breemen et al. because the claims in the present application would have been obvious and within the skill of the art. According to the Examiner, although the reference is "silent to the use of inert

materials other than polyimide on the probe", glass and ceramic materials "are effective variables for their well known properties of inertness and durability."

Applicants respectfully traverse this objection because obviousness is not established. To establish a prima facie case of obviousness, there must be at least the suggestion or motivation to modify the claims in the prior art to resemble the claims in the present application. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). No such suggestion of modification is expressed in the Van Breemen reference, nor is there any discussion of the relevant properties of the polyimide tip that would make the modification implicit. Thus, it would be improper to conclude that the claims of the present application fail for obviousness in following such a suggestion.

Even if the modification in the present claims was regarded as a simple substitution of materials, such an argument would still not establish obviousness. First, the purposes of the equivalent materials in the prior art and the present application are patentably distinct, and therefore the substitution does not establish obviousness. See *Laitram Corp. v. Deepsouth Packing Co.*, 443 F.2d 928, 170 U.S.P.Q. 190 (5th Cir. 1971). Indeed, Van Breemen does not articulate the reason for using the polyimide tip, whereas the present application articulates the method by which different non-metallic surfaces can be used to desorb and ionize specific analytes. Secondly, the mere possibility that the substitution could have been made is insufficient to establish obviousness. Although the possibility of the substitution is not explicit in the prior art, it must at least be reasonable to assume that a person "skilled in the art" would have known to make the substitution. See *National Research Development Corp. v. Varian Associates*, 822 F.Supp. 1121, 1128, 28 USPQ2d 1436 (D.N.J. 1993). It is not clear that such a person would have sufficient information to substitute the polyimide tip in the Van Breemen reference with the correct type of non-metallic surface for a given analyte necessary to achieve the affinity-directed desorption claimed in the present application.

The present case is distinguishable from the *Boesch* case cited by Examiner in that it involved merely the manipulation of a numerical value in a manufacturing process, and thus is not analogous to the modification in the present application. As previously stated, Van Breemen does not articulate the reasoning for his selection of the polyimide tip, and thus it would not be proper to speculate on the relevant property that the current claims would be optimizing. Moreover, the modifications in the present application do not merely reflect the

optimization of a known variable but instead involve a completely different mechanism by which desorption of the analyte is promoted. Therefore, the rejection of the dependent claims is improper, and withdrawal of the rejection is respectfully requested.

## CONCLUSION

Applicants believe that there is no additional fee required to file this paper. If the Applicant is in error, the Commissioner is hereby authorized to charge any required fees and/or credits by this paper and during the entire pendency of this application to Account No. 06-2375/09306611.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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Respectfully submitted,

By

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**APPENDIX 1—Version of Claims Marked to Show Changes**

49. (Amended Thrice) A method of desorbing a macromolecular analyte from a probe surface comprising the steps of:

a) providing a probe that is removably insertable into a mass spectrometer, the probe having a surface for presenting the macromolecular analyte to at least one~~a~~ single energy source that emits energy capable of desorbing and ionizing the macromolecular analyte from the probe for analyte detection, wherein at least the surface comprises a non-metallic-material selected from the group consisting of glass, ceramic, polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran~~, and the analyte is associated with a matrix material for promoting desorption and ionization of said analyte on the surface~~; and

b) exposing the macromolecular analyte on the probe surface ~~and matrix material~~ to energy from ~~the~~ at least one single energy source, whereby the macromolecular analyte is desorbed and ionized.

50. (Amended Twice) The method of claim 49 wherein the energy source emits laser light that desorbs and ionizes the macromolecular analyte to produce an ion.

51. (Amended Twice) The method of claim 50 further comprising after step (b) the steps of:

c) modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface; and

d) repeating step (b).

52. (Amended Twice) The method of claim 50 wherein the probe surface comprises an array of locations, each location having at least one macromolecular analyte deposited thereon; and step (b) comprises desorbing and ionizing a first macromolecular analyte from a first location in the array;

and wherein the method further comprises the step of (c) desorbing and ionizing a second macromolecular analyte, from a second location in the array.

53. (Amended Twice) The method of claim 50 further comprising before step (b) the step of modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface.

63. (Amended Twice) The method of claim 50 wherein the macromolecular analyte comprises a protein or a peptide.

64. (Amended Thrice) A system for detecting an macromolecular analyte comprising:

a removably insertable probe having a surface for presenting the macromolecular analyte to at least one~~a~~ single energy source that emits energy capable of desorbing and ionizing the macromolecular analyte from the probe, wherein at least the surface comprises a non-metallic material selected from the group consisting of glass, ceramic polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran,~~, and the analyte is associated with a matrix material for promoting desorption and ionization of said analyte on the surface~~;

at least one~~a~~ single energy source that directs energy to the probe surface for desorbing and ionizing the macromolecular analyte; and

a detector in communication with the probe surface that detects the desorbed macromolecular analyte.

65. (Amended Once) The system of claim 64 which is a laser desorption mass spectrometer wherein:

the energy source emits laser light that desorbs and ionizes the macromolecular analyte to produce an ion,

the system further comprises means for accelerating the ion to the detector,

the detector detects the ion, and

the system further comprises means for determining the mass of the ion.

71. (Amended Once) The system of claim 64 further comprising means for accelerating the desorbed macromolecular analyte to the detector.

86. (Amended Thrice) A method for detecting a macromolecular analyte comprising the steps of:

a) providing a system comprising:

(1) a removably insertable probe having a surface for presenting the macromolecular analyte to at least ~~a~~ one single energy source that emits energy capable of desorbing and ionizing the macromolecular analyte from the probe, wherein at least the surface ~~comprising~~ comprisesa non-metallic material selected from the group consisting of glass, ceramic polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran,wherein the macromolecular analyte is presented on the probe surface;~~, and the analyte is associated with a matrix material for promoting desorption and ionization of said analyte on the surface;~~

(2) at least ~~a~~ one single energy source that directs energy to the probe surface for desorbing and ionizing the macromolecular analyte; and

(3) a detector in communication with the probe surface that detects the desorbed and ionized macromolecular analyte;

b) desorbing and ionizing at least a portion of the macromolecular analyte from the surface by exposing the macromolecular analyte to energy from ~~the~~ at least one single energy source; and

c) detecting the desorbed and ionized macromolecular analyte with the detector.

87. (Amended Twice) The method of claim 86 wherein the system is a laser desorption mass spectrometer wherein the energy source emits laser light that desorbs and ionizes the macromolecular analyte to produce an ion, the detector detects the ion and the system further comprises means for accelerating the ion to the detector, and the method further comprises determining the mass of the ion.

88. (Amended Twice) The method of claim 87 further comprising before step (b) the step of modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface.

89. (Amended Twice) The method of claim 87 further comprising after step (c) the steps of:

d) modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface; and

e) repeating steps b) and c).

90. (Amended Twice) The method of claim 87 wherein the probe surface comprises an array of locations, each location having at least one macromolecular analyte deposited thereon; and step (b) comprises desorbing and ionizing a first macromolecular analyte from a first location in the array;

and wherein the method further comprises the step of:

d) desorbing and ionizing a second macromolecular analyte from a second location in the array; and

e) detecting the desorbed and ionized second macromolecular analyte with the detector.

91. (Amended Once) The method of claim 87 further comprising the step of displaying the determined mass of the macromolecular analyte.

101. (Amended Once) The method of claim 87 wherein the macromolecular analyte comprises a protein or a peptide.

105. (Amended Once) The method of claim 50, wherein the macromolecular analyte is a biomolecule.

106. (Amended Once) The method of claim 50, wherein the macromolecular analyte is a biomolecule from an undifferentiated sample.

107. (Amended Once) The method of claim 50, wherein the macromolecular analyte is a nucleic acid.

108. (Amended Once) The system of claim 65, wherein the macromolecular analyte is a biomolecule.

109. (Amended Once) The system of claim 65, wherein the macromolecular analyte is a biomolecule from an undifferentiated sample.

110. (Amended Once) The system of claim 65, wherein the macromolecular analyte is a protein or a peptide.

111. (Amended Once) The method of claim 87, wherein the macromolecular analyte is a biomolecule.

112. (Amended Once) The method of claim 87, wherein the macromolecular analyte is a biomolecule from an undifferentiated sample.

113. (Amended Once) The method of claim 87, wherein the macromolecular analyte is a protein or a peptide.

120. (Amended Once) The method of claim 50, wherein the macromolecular analyte is a carbohydrate.

121. (Amended Once) The system of claim 65, wherein the macromolecular analyte is a nucleic acid.

122. (Amended Once) The system of claim 65, wherein the macromolecular analyte is a carbohydrate.

123. (Amended Once) The method of claim 87, wherein the macromolecular analyte is a nucleic acid.

124. (Amended Once) The method of claim 87, wherein the macromolecular analyte is a carbohydrate.

49. A method of desorbing a macromolecular analyte from a probe surface comprising the steps of:

a) providing a probe that is removably insertable into a mass spectrometer, the probe having a surface for presenting the macromolecular analyte to at least one single energy source that emits energy capable of desorbing and ionizing the macromolecular analyte from the probe for analyte detection, wherein at least the surface comprises a non-metallic-material selected from the group consisting of glass, ceramic, polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran; and

b) exposing the macromolecular analyte on the probe surface to energy from at least one single energy source, whereby the macromolecular analyte is desorbed and ionized.

50. The method of claim 49 wherein the energy source emits laser light that desorbs and ionizes the macromolecular analyte to produce an ion.

51. The method of claim 50 further comprising after step (b) the steps of:

c) modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface; and

d) repeating step (b).

52. The method of claim 50 wherein the probe surface comprises an array of locations, each location having at least one macromolecular analyte deposited thereon; and step (b) comprises desorbing and ionizing a first macromolecular analyte from a first location in the array;

and wherein the method further comprises the step of (c) desorbing and ionizing a second macromolecular analyte, from a second location in the array.

53. The method of claim 50 further comprising before step (b) the step of modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface.

56. The method of claim 50 wherein the non-metallic material is substantially porous.

57. The method of claim 50 wherein the non-metallic material is substantially non-porous.

60. The method of claim 50 wherein the probe comprises glass.

61. The method of claim 50 wherein the probe comprises ceramic.

63. The method of claim 50 wherein the macromolecular analyte comprises a protein or a peptide.

64. A system for detecting an macromolecular analyte comprising:

a removably insertable probe having a surface for presenting the macromolecular analyte to at least one single energy source that emits energy capable of desorbing and ionizing the macromolecular analyte from the probe, wherein at least the surface comprises a non-metallic material selected from the group consisting of glass, ceramic, polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran;

at least one single energy source that directs energy to the probe surface for desorbing and ionizing the macromolecular analyte; and

a detector in communication with the probe surface that detects the desorbed macromolecular analyte.

65. The system of claim 64 which is a laser desorption mass spectrometer wherein:

the energy source emits laser light that desorbs and ionizes the macromolecular analyte to produce an ion,

the system further comprises means for accelerating the ion to the detector,

the detector detects the ion, and

the system further comprises means for determining the mass of the ion.

66. The system of claim 64 wherein the energy source emits laser light.

67. The system of claim 64 wherein the energy source emits plasma energy or fast atoms.

68. The system of claim 64 wherein the energy source emits energy of a variety of wavelengths.

69. The system of claim 64 wherein the detector detects ions.

70. The system of claim 64 wherein the detector detects radioactivity or light.

71. The system of claim 64 further comprising means for accelerating the desorbed macromolecular analyte to the detector.

75. The system of claim 65 wherein the non-metallic material is substantially porous.

76. The system of claim 65 wherein the non-metallic material is substantially non-porous.

79. The system of claim 65 wherein the probe comprises glass.

80. The system of claim 65 wherein the probe comprises ceramic.

82. The system of claim 75 wherein the porous material comprises sponge-like, polymeric, high surface areas.

83. The system of claim 76 wherein the non-porous material is selected from the group consisting of glass and polyacrylamide.

86. A method for detecting a macromolecular analyte comprising the steps of:

a) providing a system comprising:

(1) a removably insertable probe having a surface for presenting the macromolecular analyte to at least one single energy source that emits energy capable of desorbing and ionizing the macromolecular analyte from the probe, wherein at least the surface comprises a non-metallic material selected from the group consisting of glass, ceramic, polystyrene, polypropylene, polyethylene, polycarbonate, nylon, starch, agarose, and dextran, wherein the macromolecular analyte is presented on the probe surface,

(2) at least one single energy source that directs energy to the probe surface for desorbing and ionizing the macromolecular analyte; and

(3) a detector in communication with the probe surface that detects the desorbed and ionized macromolecular analyte;

b) desorbing and ionizing at least a portion of the macromolecular analyte from the surface by exposing the macromolecular analyte to energy from at least one single energy source; and

c) detecting the desorbed and ionized macromolecular analyte with the detector.

87. The method of claim 86 wherein the system is a laser desorption mass spectrometer wherein the energy source emits laser light that desorbs and ionizes the macromolecular analyte to produce an ion, the detector detects the ion and the system further comprises means for accelerating the ion to the detector, and the method further comprises determining the mass of the ion.

88. The method of claim 87 further comprising before step (b) the step of modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface.

89. The method of claim 87 further comprising after step (c) the steps of:

d) modifying the macromolecular analyte chemically or enzymatically while deposited on the probe surface; and

e) repeating steps b) and c).

90. The method of claim 87 wherein the probe surface comprises an array of locations, each location having at least one macromolecular analyte deposited thereon; and step (b) comprises desorbing and ionizing a first macromolecular analyte from a first location in the array;

and wherein the method further comprises the step of:

d) desorbing and ionizing a second macromolecular analyte from a second location in the array; and

e) detecting the desorbed and ionized second macromolecular analyte with the detector.

91. The method of claim 87 further comprising the step of displaying the determined mass of the macromolecular analyte.

94. The method of claim 87 wherein the non-metallic material is substantially porous.

95. The method of claim 87 wherein the non-metallic material is substantially non-porous.

98. The method of claim 87 wherein the probe comprises glass.

99. The method of claim 87 wherein the probe comprises ceramic.

101. The method of claim 87 wherein the macromolecular analyte comprises a protein or a peptide.

105. The method of claim 50, wherein the macromolecular analyte is a biomolecule.

106. The method of claim 50, wherein the macromolecular analyte is a biomolecule from an undifferentiated sample.

107. The method of claim 50, wherein the macromolecular analyte is a nucleic acid.

108. The system of claim 65, wherein the macromolecular analyte is a biomolecule.

109. The system of claim 65, wherein the macromolecular analyte is a biomolecule from an undifferentiated sample.

110. The system of claim 65, wherein the macromolecular analyte is a protein or a peptide.

111. The method of claim 87, wherein the macromolecular analyte is a biomolecule.

112. The method of claim 87, wherein the macromolecular analyte is a biomolecule from an undifferentiated sample.

113. The method of claim 87, wherein the macromolecular analyte is a protein or a peptide.

120. The method of claim 50, wherein the macromolecular analyte is a carbohydrate.

121. The system of claim 65, wherein the macromolecular analyte is a nucleic acid.

122. The system of claim 65, wherein the macromolecular analyte is a carbohydrate.

123. The method of claim 87, wherein the macromolecular analyte is a nucleic acid.

124. The method of claim 87, wherein the macromolecular analyte is a carbohydrate.

125. The method of claim 49 further comprising the macromolecular analyte associated with a matrix material for promoting desorption and ionization of the macromolecular analyte on the surface.

126. The method of claim 64 further comprising the macromolecular analyte associated with a matrix material for promoting desorption and ionization of the macromolecular analyte on the surface.

127. The method of claim 86 further comprising the macromolecular analyte associated with a matrix material for promoting desorption and ionization of the macromolecular analyte on the surface.

128. The method of claim 49 wherein the non-metallic material is glass.

129. The method of claim 49 wherein the non-metallic material is ceramic.

130. The method of claim 49 wherein the non-metallic material is polystyrene.

131. The method of claim 49 wherein the non-metallic material is polypropylene.

132. The method of claim 49 wherein the non-metallic material is polycarbonate.

133. The method of claim 49 wherein the non-metallic material is nylon.

134. The method of claim 49 wherein the non-metallic material is dextran.

135. The system of claim 64 wherein the non-metallic material is glass.

136. The system of claim 64 wherein the non-metallic material is ceramic.

137. The system of claim 64 wherein the non-metallic material is polystyrene.

138. The system of claim 64 wherein the non-metallic material is polypropylene.

139. The system of claim 64 wherein the non-metallic material is polycarbonate.

140. The system of claim 64 wherein the non-metallic material is nylon.

141. The system of claim 64 wherein the non-metallic material is dextran.

142. The method of claim 86 wherein the non-metallic material is glass.

143. The method of claim 86 wherein the non-metallic material is ceramic.

144. The method of claim 86 wherein the non-metallic material is polystyrene.

145. The method of claim 86 wherein the non-metallic material is polypropylene.

146. The method of claim 86 wherein the non-metallic material is polycarbonate.

147. The method of claim 86 wherein the non-metallic material is nylon.

148. The method of claim 86 wherein the non-metallic material is dextran.